IV. Regulations controlling the sale of mild analgesics in Canada

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Summary: Some mild analgesic preparations are sold only on prescription; others are required to carry specific label warnings. The conditions of sale of some are further restricted by limitations on their dose. The "prescription only" sale of both phenacetin and acetaminophen would leave no "over-the-counter" analogies available for individuals sensitive to salicylates. Since analgesic nephropathy results from long-term abuse of these preparations, the need is to prevent abuse without inhibiting their proper use.

The toxicity of mild analgesics and especially their effects on the kidney have been of concern to the Department of National Health and Welfare for some time. We have reviewed the literature, assessed the effectiveness of regulatory actions taken in other countries and conducted toxicity studies in laboratory animals and some studies in man.

Present regulations in Canada

The present regulations governing the sale of preparations containing mild analgesics of the ASA, phenacetin or acetaminophen type can be divided into four main categories:

1: Preparations sold only on prescription. These are mixtures which in addition to mild analgesics contain such drugs as propoxyphene, barbiturates, meperamabate or more than ¼ grain of codeine. The largest group in this category consists of APC preparations with more than ½ grain of codeine.

2: Preparations sold "over-the-counter" which cannot be advertised to the public and which must be labelled "To be used only on the advice of a physician". These are preparations containing amounts of drugs in excess of those listed in the Table of Limits of the Food and Drug Regulations. This Table contains a number of drugs including ASA, phenacetin and acetaminophen. Any preparation which contains a single or daily dose in excess of that specified in the Table cannot be advertised to the public and the label must carry a warning that the product is to be used only on the advice of a physician (Table I).

3: Preparations sold "over-the-counter" which can be advertised to the public (i.e. those which contain quantities of drugs smaller than those listed in the Table of Limits).

4: Preparations sold "over-the-counter" under the Proprietary or Patent Medicine Act.

There is a great similarity in the composition of the products in the last two groups. Both include numerous APC preparations. However, products sold under the Proprietary or Patent Medicine Act cannot contain codeine or acetaminophen.
The Proprietary or Patent Medicine Act was established in 1908 to regulate the sale and manufacture of so-called patent medicines. It was originally enacted to protect the consumer from buying worthless wares under the guise of packaged medicines. Nowadays its purpose is to ensure that home medication for the symptomatic relief of minor ailments is safe and effective when used according to the directions supplied with the package, and that the preparation contains no ingredient that may be harmful or potentially dangerous for self-medication. Under most provincial Pharmacy Acts these preparations may be sold in supermarkets and grocery stores as well as in drug stores. They are sold “over-the-counter” and are often widely advertised to the public.

Special warning statements are required on preparations containing phenacetin and ASA and also on some of the now rarely-used mild analgesics such as aminopyrine and dipryrone. All preparations containing phenacetin must carry a warning on the label stating: “Caution: May be injurious if taken in large doses or for a long time. Do not exceed the recommended dose without consulting a physician.”

Warning statements required for preparations containing acetylsalicylic acid and its salts are directed towards the prevention of accidental poisoning of children and do not refer to any specific toxicity of such preparations.

Table I
Extract from the Table of Limits of drug dosage

<table>
<thead>
<tr>
<th>Drug</th>
<th>Single dose (mg.)</th>
<th>Daily dose (mg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>975</td>
<td>2925</td>
</tr>
<tr>
<td>Phenacetin</td>
<td>650</td>
<td>1950</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>325</td>
<td>975</td>
</tr>
</tbody>
</table>

Table II
Analgesic preparations available in Canada

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Single ingredient preparations</th>
<th>Mixtures containing more than one active ingredient</th>
<th>Sold on prescription only</th>
<th>Sold under P or PM Act</th>
<th>Total no. of preparations available</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>140</td>
<td>530</td>
<td>142</td>
<td>130</td>
<td>670</td>
</tr>
<tr>
<td>Phenacetin</td>
<td>1</td>
<td>410</td>
<td>104</td>
<td>83</td>
<td>411</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>9</td>
<td>58</td>
<td>15</td>
<td>—</td>
<td>77</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>16</td>
<td>14</td>
<td>30</td>
<td>—</td>
<td>30</td>
</tr>
</tbody>
</table>

There are no special cautionary statements required for acetaminophen preparations but the use of this drug is to some extent limited by the low level in the Table of Limits and by the fact that it is not permitted in preparations registered under the Proprietary or Patent Medicine Act.

In spite of these restrictions and label warnings these analgesics are freely available to the public and are widely used (Table II).

Several surveys have shown that many people take analgesics regularly without a good medical reason. This habit is apparently widespread throughout the world. In one survey conducted in the United Kingdom approximately 4,500,000 people said they took an analgesic at least once a week. About 1,200,000 people said they took analgesics every day; two thirds took them without a prescription. There were about 500,000 people taking an average of over five tablets or powders every day; nearly half did so without a prescription.

Regulations in other countries
Since 1961 phenacetin and acetaminophen have been obtainable only by prescription in Sweden and Denmark. We understand that the sales of these products have decreased substantially and that there has been a corresponding decrease in the incidence of analgesic nephropathy.

In Australia where both the sale of “O.T.C.” analgesics and the incidence of analgesic nephropathy are very high, phenacetin has been removed from the National Health Service listing. However, this has apparently resulted in the replacement of phenacetin with acetaminophen by many pharmaceutical manufacturers. Some patients who had previously been persuaded to give up analgesics began to take the new preparations, having been assured by doctors, chemists or advertisements that these were safe. This resulted in a recrudescence of their renal pathology.

In the United Kingdom acetaminophen (paracetamol) has over the past few years become a popular analgesic and has to a large extent replaced phenacetin. Nevertheless no warnings are currently required on the label of any analgesic sold there.

In the United States the following statement is required on all preparations containing phenacetin: “This medication may damage the kidneys when used in large amounts or for a long period of time. Do not take more than the recommended dose, nor take regularly for longer than 10 days without consulting your physician.” All preparations containing acetaminophen must carry the following statement: “Do not give to children under three years of age or use for more than 10 days without consulting a physician.” In addition, all preparations containing acetaminophen or ASA, when recommended for use in arthritis, must carry the following statement: “If pain persists for more than 10 days, or if redness is present, or in conditions affecting children under 12 years of age, consult a physician immediately.”

It is interesting to note that AMA Drug Evaluations published by the Council on Drugs of the American Medical Association contains the following statement: “Phenacetin has been implicated as a cause of nephrotoxicity, which has been reported to occur with chronic abuse of analgesic mixtures, but there is little evidence for singling out phenacetin as the offending agent.”

The Council also suggests that there is no conclusive evidence that APC is clinically superior to ASA alone.

Possible future regulations in Canada
In Canada the Health Protection Branch of the Department of National Health and Welfare has been considering whether or not there is a need for restricting the ready availability of analgesic preparations and, if so, how it should be done. Several courses of action are available:

1. Maintain existing regulations governing the sale and labelling of analgesics.
2. Change labelling requirements: (a) strengthen label warnings for phenacetin (b) add label warning for acetaminophen (c) add label warning for all O.T.C. analgesic mixtures.

3. Require manufacturers to reformulate analgesic mixtures, removing phenacetin and acetaminophen, and ensuring that phenacetin is not replaced by acetaminophen.

4. Remove phenacetin from all preparations registered under the Proprietary or Patent Medicine Act and continue to prohibit the presence of acetaminophen in such preparations.

5. Include phenacetin in Schedule F of the regulations under the Food and Drugs Act (prescription only).

6. Include both phenacetin and acetaminophen in Schedule F.

7. Remove phenacetin from the market entirely.

There are disadvantages to each course of action. For example:

1. Putting phenacetin on prescription could have certain disadvantages: (a) Manufacturers might replace phenacetin with higher doses of ASA, remove the warning from the label and advertise the new formula as "now safer". This might result in an increase in adverse reactions affecting the gastrointestinal tract. (b) Manufacturers might replace phenacetin with acetaminophen and remove the label warning. (c) Patients with renal damage who had been persuaded to stop abusing analgesics might abuse these reformulated mixtures.

2. If both phenacetin and acetaminophen were placed on prescription, ASA and salicylaldehyde would be virtually the only remaining analgesics available without prescription, and allergy and gastrointestinal intolerance to salicylates are a problem in a significant number of people.

When considering the need for tighter controls over the sale of phenacetin and other analgesics it should be borne in mind that analgesic nephropathy is essentially a disease of people who abuse analgesics. The need therefore is to control abuse rather than normal use.

Résumé

Les règlements relatifs à la vente des analgésiques faibles au Canada

Certains analgésiques bénins ne peuvent se vendre que sur présentation d'une prescription. Pour d'autres, on exige que l'étiquette porte des avertissements spécifiques. Les conditions de vente de certains produits sont frappées d'autres restrictions, portant sur une limitation de la dose. La vente de la phénacétine et de l'acétaminophène limitée par la mention "Prescription obligatoire" ne laisserait aucune possibilité aux individus sensibles aux salicylates de se procurer "librement" un analgésique. Comme leur abus prolongé se traduit par une néphropathie analgésique, le problème qui se pose est de chercher à prévenir l'abus de ces préparations, sans pour autant empêcher un usage raisonnable.

References

1. Is aspirin safe? Pharm J 207: 482, 1971

Renal pelvic tumour associated with analgesic abuse


An association between renal pelvic tumour and analgesic abuse was first reported in 1965 by Swedish investigators. Apart from two later Swedish studies, a recent report from Denmark, we found no other documented cases. The following case is the first reported in North America.

Case history

The patient, a 69-year-old woman, presented in February 1970 with a two-week history of epigastric pain and melena. Past illnesses included pneumonia in 1944, meales in 1953, retrobulbar neuritis in 1965 and attacks of paroxysmal atrial tachycardia for many years. She admitted to an excessive consumption of analgesics for 20 years—15 to 20 tablets daily of aspirin, phenacetin, caffeine and codeine for aches and pains. Her alcohol intake was also excessive and she smoked a packet of cigarettes a day.

Physical examination demonstrated epigastric tenderness. Results of laboratory investigations were as follows: Hb 12.3 g./100 ml., falling to 10.8 g./100 ml. over the next few days, serum creatinine 1.2 mg./100 ml. and normal BUN and electrolytes. A gastrointestinal series revealed an antral ulcer. Routine urinalysis showed a trace of albumin with 15 to 20 leucocytes per high power field. Urine culture showed no growth of organisms. The creatinine clearance was 57.2 ml./min. The specific gravity of urine after 12 hours dehydration was 1.007; 24-hour urine collections contained 137 to 431 mg. of protein and 216 mg. of uric acid. An intravenous pyelogram revealed bilateral papillary necrosis with two radiolucent filling defects in the left renal pelvis which were thought to be necrotic papillae. A biopsy of the right kidney showed interstitial fibrosis, inflammatory cells and tubular atrophy.

The gastric ulcer responded well to conservative therapy and the patient was discharged. She was kept under observation and at this time was asymptomatic. Laboratory investigations revealed an erythrocyte sedimentation rate of 77 mm. in 1 hr. and microscopic hematuria. The filling defects in the left renal pelvis had increased in size (Fig. 1) and urine cytology was positive for malignant cells. A left nephro-ureterectomy was performed. At operation there was no evidence of secondary spread or involvement of the ureter. Pathological study showed an irregular renal pelvic calyeal pattern, evidence of diffuse interstitial fibrosis compatible with phenacetin nephropathy, and three small Grade III transitional cell carcinomas of the renal pelvis (Fig. 2).

The patient at present remains asymptomatic with a serum creatinine of 1.4 mg./100 ml. Urine cytology and cystoscopy are being performed at regular follow-up visits.

Comment

The syndrome of analgesic abuse is being recognized more frequently but